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Calibration of a prototype NIRS oximeter against two commercial devices on a blood-lipid phantom

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Abstract: In a blood-lipid liquid phantom the prototype near-infrared spectroscopy oximeter OxyPrem was calibrated against the INVOS® 5100c adult sensor in respect to values of regional tissue oxygen haemoglobin saturation ($rStO_2$) for possible inclusion in the randomised clinical trial - SafeBoosC. In addition different commercial NIRS oximeters were compared on changing haemoglobin oxygen saturation and compared against co-oximetry. The best calibration was achieved with a simple offset and a linear scaling of the OxyPrem $rStO_2$ values. The INVOS adult and pediatric sensor gave systematically different values, while the difference between the NIRO® 300 and the two INVOS sensors were magnitude dependent. The co-oximetry proved unreliable on such low haemoglobin and high Intralipid levels.

OCIS codes: (170.1470) Blood or tissue constituent monitoring; (300.6190) Spectrometers.

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1. Introduction

Near infrared spectroscopy (NIRS) enables non-invasive measurement of the regional tissue oxygen haemoglobin saturation ($rStO_2$). $rStO_2$ is correlated to both arterial (SaO_2) and venous oxygen haemoglobin saturation (SvO_2) [1] and is an estimate of the local oxygen balance, i.e. the oxygen delivery - oxygen consumption difference. The randomised clinical trial (RCT) SafeBoosC (Safeguarding the Brains Of Our Smallest Children) hypothesises that cerebral NIRS oximetry monitoring during the first three days of life of the extremely preterm infants can improve outcome [2]. The normal range of $rStO_2$ in preterm infants is 55-85% as determined by the commercial device INVOS® 5100c using the adult sensor [3].

As a part of the SafeBoosC project, a prototype NIRS device 'OxyPrem' dedicated to the preterm infant head has been developed with the aim of combining reusable sensor technology with higher precision [2].

Validation of NIRS oximetry is difficult, as no reference standard exists. *In-vivo* it is usually validated by comparison of $rStO_2$ with a weighted mean of SaO_2 and SvO_2 [4–10]. This method has limitations as it includes the imprecision of NIRS re-siting, the errors of measurement on SaO_2 and SvO_2, as well as extra-cerebral contribution to jugular venous blood. Furthermore, the arterial to venous volume ratios may be changing dependent on the level of oxygenation. *In-vitro* testing on solid state or liquid phantoms has the advantage of controllable optical properties and less variation [11,12].

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The present study had three objectives: 1) to calibrate the prototype OxyPrem against the INVOS® 5100c adult sensor for possible inclusion in the SafeBoosC trial; 2) to compare different commercial NIRS oximeters on changing haemoglobin oxygen saturation on a blood-lipid liquid phantom; 3) to compare the oximeters against co-oximetry.

2. Methods

2.1 Phantom

The blood-lipid phantom consisted of a mixture of isotonic saline, erythrocyte suspension and Intralipid® 200 mg/ml. The erythrocyte suspension is made from human blood drawn into a citrate phosphate dextrose solutution that is centrifuged. The erythrocytes are finally suspended in a saline, adenine, glucose, and mannitol solution (SAG-M) to a hematocrit of about 64%. The mixture was 0.5% (5 mg fat/ml) Intralipid and a haematocrit of 1.5. It was contained in a five-litre bucket with a diameter of 17.5 cm. The NIRS sensors were equally distributed along the wall (Fig. 1) ensuring a distance of at least 8 cm from light sources and light detectors of different devices. The bucket was covered with a plastic film. The reduced scattering coefficient μ_s' of 0.5% Intralipid® is about 0.5 mm^{-1} [13–16]. This is similar to scattering properties of the neonatal head [17,18]. Estimates of cerebral blood volume (CBV) in neonates vary considerably between studies ranging from 1.7 to 3.7 ml/100 g in primarily preterm populations [19–25], this corresponds to a 'tissue haematocrit' about 1.0 - 1.5% if blood haematocrit is 45% [26] and the specific gravity of brain tissue is 1.05 g/ml.

The solution was pumped through an extracorporeal membrane oxygenator (STÖKERT SIII) with a servo-controlled heater maintaining a temperature of 37.5 °C. The flow on the pump was 1 litre per minute, and the fluid in the bucket was additionally circulated by a magnet stirrer (KEBO-Lab MR 2000). The gas flow to the membrane oxygenator consisted of a variable mixture of oxygen, nitrogen, and CO_2 (Fig. 2). pH was kept about 7.4 by titration of sodium bicarbonate 1 mmol/ml.

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Fig. 1. The blood-lipid phantom seen from above before the fluid level was increased to well above the sensor level. The sensors are from the top and clock-wise: OxyPrem 1, OxyPrem 2, INVOS adult, NIRO, and INVOS pediatric. Only OxyPrem 2 was used for data collection. The tubings to and from the oxygenator were placed on both sides of the OxyPrem 1.

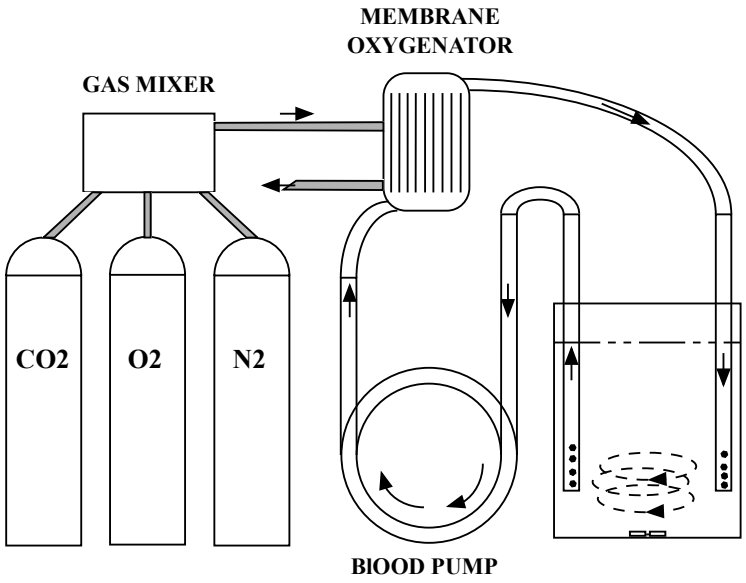

Fig. 2. A schematic presentation of the phantom setup. White tubes contain blood. Gray tubes contain gas. The NIRS sensors and the heat exchanger are not presented in the diagram.

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2.2 NIRS devices

INVOS® 5100c uses one LED light source with wavelengths 730 and 810 nm and two light detectors, three and four centimeters from the source, respectively. This geometry is identical for the adult, the pediatric, and the neonatal sensor.

NIRO 300 employs spatially resolved spectroscopy with lasers with wavelengths of 775, 810, 847, and 919 nm. The light absorption coefficient is estimated by the decrease in reflected light as a function of distance from light source. By assuming a semi-infinite medium, knowing the wavelength dependence of the reduced scattering coefficient, then the spectral shape of the absorption coefficient can be calculated and the $rStO_2$ estimated. In contrast to the INVOS, this algorithm was published [12,27]. Two light detectors are placed respectively 3.6 and 4.4 cm from the source.

OxyPrem is designed and manufactured by the Biomedical Optics Research Laboratory (BORL) of the Division of Neonatology at the University Hospital Zurich, Switzerland. It applies four light sources with three light emitting diodes with nominal wavelengths of 760 nm, 805 nm, and 870 nm, and two detectors. The pair-wise source-detector separation is 1.5 and 2.5 cm. It employs a self-calibrating principle [28] using multiple light paths, which has proven to be advantageous [29].

In present study the INVOS adult sensor (SAFB-SM), the INVOS pediatric sensor (SPFB), the NIRO 300 sensor with detector at 3.6 and 4.4 cm from the source, and the OxyPrem sensor were used (Fig. 1).

2.3 Blood sampling

Blood for reference SO_2 was drawn from the circuit before the oxygenator and analysed on an ABL-800® by co-oximetry. Part of each blood sample was immediately analysed for pH, pO_2 and pCO_2, while the remains were spun. The precipitate containing the erythrocytes was then analysed for SO_2. Differences in partial pressures of the two analyses served as quality control. This method was developed, as the ABL-800 cannot measure SO_2 in a solution with an extremely low haemoglobin concentration and extremely high turbidity due to Intralipid.

2.4 Experimental procedure

Initially the phantom was oxygenated by flow of pure oxygen through the membrane oxygenator. This ensured theoretical baseline haemoglobin saturation very close to 100%. Next the oxygen was turned off and replaced by pure nitrogen flow to the oxygenator. This should lower the phantom oxygen content depending on the oxygen consumption of the blood and the oxygen contamination from outside the circuit. Lastly gas flow to the oxygenator was shifted back to pure oxygen, while the blood pump was stopped intermittently.

2.5 Statistical analysis

The blood sample pO_2-SO_2 pairs were fitted to the Hill's equation [30] by the Nelder-Mead simplex algorithm with an initial estimate of coefficients of $K = 1$ and $\alpha = 1$. Pre-spin SO_2 were calculated from the derived dissociation curve. Pairwise device comparisons with simple linear regression and all instruments were compared with the reference blood samples. All data handling was done in Matlab R2012b (Mathworks, Inc, Mass., USA).

2.6 Calibration of OxyPrem

For the SafeBoosC trial it is beneficial to have as little variability as possible caused by different measurement characteristics of different NIRS devices. Therefore we used the present experiment to determine a transformation of $rStO_2$ values to make OxyPrem measure as similarly to the INVOS 5100c Adult SomaSensor as possible.

If it is assumed that the present phantom constitutes a homogenous, semi-infinite medium differences between devices could derive from different basic assumptions of water content

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and scattering properties [31]. It is not publically known what is assumed in the INVOS algorithm.

The 'pre-calibration' SO_2 values are based on the assumptions of 0% water and μ_s' of 0.5% Intralipid® while using absorption coefficients measured by Matcher et al. [27] and weighted with known LED spectra.

In order to achieve OxyPrem SO_2 values comparable to the INVOS Adult SomaSensor the assumptions of water content and scattering properties were systematically varied. For this, 21 values from different saturations distributed approximately equally throughout the 16-94% range of the INVOS® adult sensor were chosen. Then a residual R was calculated as a squared sum of differences for several criteria m: OxyPrem SO_2 - INVOS values, tHb - actual haemoglobin content and deviation from linear wavelength dependence of μ_s'.

$$R = \sum_{i=1}^{i=21} \sum_{m=1}^{m=3} w_{\text{criterion}\,m} (\Delta\text{criterion}_{\text{m}}[i])^2 \qquad (1)$$

Then R was minimized in a bounded minimum search using the 'Nelder-Mead simplex direct search' algorithm with μ_s' for 760 nm, 805 nm, and 870 nm (all between 2 and 30 cm^{-1}) and percentage of water (between 0 and 120%) as variables. Weighting factors $w_{\text{criterion}}$ of the different criteria in the sum were each varied over several magnitudes to cover the range of one criterion only to all criteria having equal weights in the residual function. The result was in all cases either very unrealistic values for μ_s' with multiple variables in the bounds or resulting fits much worse compared to a simple linear scaling (Fig. 3).

3. Results

The calibration of the OxyPrem SO_2 using a simple linear scaling (y = 1.47x – 33.1) resulted in a good fit (R-Squared 0.97; p<0.0001) (Fig. 3).

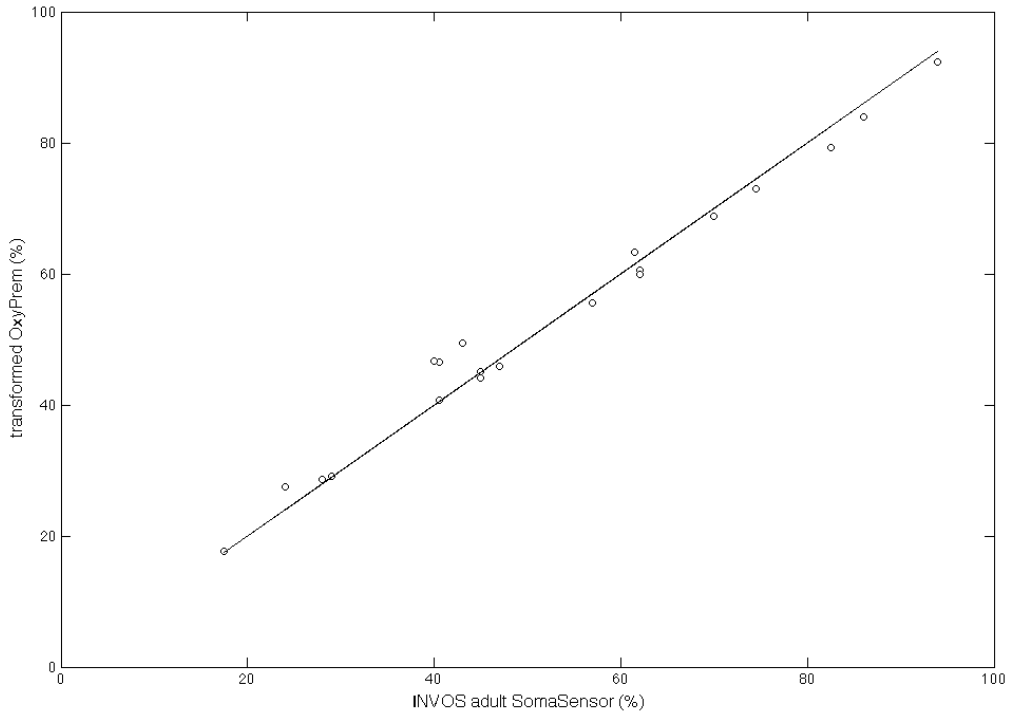

Fig. 3. Linear regression on INVOS adult SomaSensor vs. the transformed OxyPrem SO_2.

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All three commercial device/sensor combinations gave systematically different values of SO_2 (Fig. 4). The INVOS sensors showed limits of 15% and 95%.

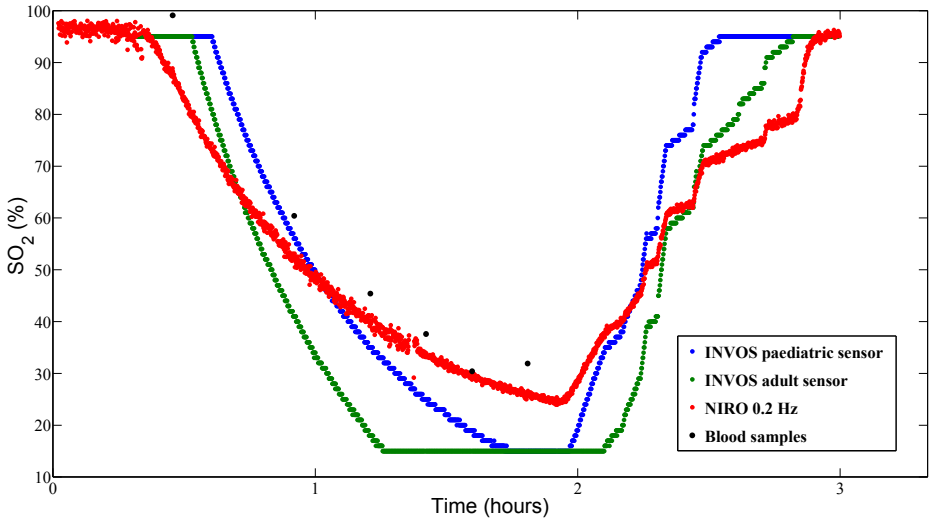

Fig. 4. Time-series of SO_2 for each of the commercial NIRS devices and the blood samples. Important aspects: SO_2 values differ in the low range between NIRO and INVOS; INVOS adult sensor has lower values than the neonatal sensor; and INVOS is clipping the values at 15% and 95%.

The INVOS adult and pediatric SomaSensors were also linearly correlated with the pediatric sensor reading systematically higher than the adult sensor (y = 0.96x + 17.91; R-square 0.99). The INVOS adult SomaSensor was also linearly correlated with the NIRO, but with a different slope (y = 0.53x + 30.45; R-square 0.98) (Fig. 5).

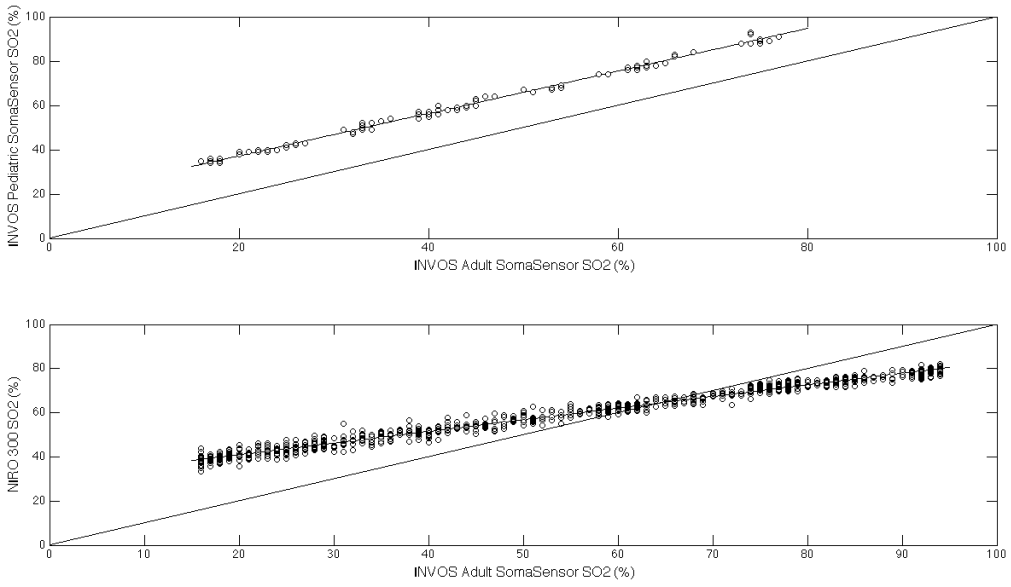

Fig. 5. Linear regression on INVOS adult SomaSensor vs. INVOS Pediatric SomaSensor (upper plot) and NIRO 300 (lower plot) SO_2, respectively.

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The co-oximetry $SO2_2$ was higher than any of the NIRS derived SO_2 values (Fig. 4). pO_2 in the blood samples decreased during spinning when the pO_2 was low before spinning, while at higher pre-spinning pO_2 the oxygen tension increased (Table 1).

Table 1. Co-oximetry Pre- and Post-spinning pO_2 and SO_2

Post-spin pO_2 (kPa)	Pre-spin pO_2 (kPa)	Difference pO_2 (kPa)	Post-spin SO_2 (%)	Estim. pre-spin SO_2 (%)*
10.4	8.5	2.0	99	95
3.1	3.4	-0.3	60	65
2.2	2.4	-0.2	38	45
1.8	2.1	-0.2	32	39
5.0	5.3	-0.3	84	86
6.9	7.0	-0.1	93	93
14.9	7.5	7.4	97	92
23.2	19.2	4.0	100	100

*Estimated from the dissocation curve from the post-spin pO_2 – SO_2 data.

4. Discussion

It was possible to do a simple linear calibration of the prototype oxymeter to the commercial reference in a lipid phantom of 0.5% Intralipid, a haematocrit of 1.5%, and haemoglobin-oxygen saturation SO_2 ranging from 30% to 100%. The INVOS 5100c Adult SomaSensor, the Pediatric SomaSensor, and the NIRO 300 gave systematically different values of SO_2. The pair-wise relations between the commercial NIRS devices were, however, also all linear.

The strength of the approach is that an estimate of the difference in absolute values are achieved on a maximum of oxygenation range, without the variation induced by different patients, sensor positions, and possibly depth of measurement. Moreover the co-oximetry is a potential reference standard not possible in *in vivo* measurements. The present phantom had optical properties simulating the neonatal head, but in future studies the effect of different scattering can be examined by changing the concentration of Intralipid.

It is a weakness that we do not now exactly how the sensors behaved when immersed in the flowing fluid. The sensors were fixated, but some movement cannot be excluded. However the impact of a slightly curving sensor on the $rStO_2$ has been shown to be minor [32]. Furthermore, the design relies on homogeneous oxygenation in the bucket. The in- and outlet from the bucket could theoretically induce heterogeneity. However moving a sensor around the rim of the bucket during mid-range steady state oxygenation gave no apparent indication of inhomogeneity. Another aspect is the violation of the semi-infinite geometry that is assumed in reflectance spectroscopy. In the present phantom the light boundaries are in essence the black rubber surrounding the detectors by more than 1 cm in the commercial devices. This material absorbs light and in that conforms to a semi-infinite boundary condition. Beyond that the light will hit the curved plastic surface of the bucket. It has been shown that the curvature has no effect, when the sensors are placed perpendicular to the curvature [33]. Although some will be reflected, this situation is not different from normal clinical use in newborns, where a bandage may be used to fix the sensor. Furthermore, it is unlikely that it will impact the $rStO_2$ estimates substantially, as the impact on light intensities at the two detectors are likely to be proportionate thus potential wavelength dependent factors levels out. At last regarding the calibration for use in neonates the lack of haemoglobin F in the phantom should be noted. The differences between the optical spectra of haemoglobin F and haemoglobin A in the near infrared range are, however, modest and that the impact on the $rStO_2$ is minor [34].

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It would have been preferable to make direct measurements of μ_s' on the phantom. However, a recent study by Di Ninni found that that the optical properties of different samples from the same batch are almost identical, inter-batch variations are small, and the optical properties remains stable over time [13].This implies that the optical characteristics deduced from previous studies are likely to be close to the actual properties.

The validation procedure, i.e. comparing the NIRS values with co-oximetry gave several problems. It was not possible to use the co-oximeter directly on samples from the phantom. The procedure of spinning the samples after a direct pO_2 measurement introduced possible oxygen contamination of the sample. The repeatability of the co-oximetry measurements were good at saturations above 95%, but due to the shape of the oxygen-hemoglobin dissocation curve it is evident that oxygen contamination impacts the saturation most at the steep part of the curve around a saturation of 50%. The fact the blood sample analysis took more than fives minutes and that the phantom could not be held steady at midrange saturations made quantification of repeatability of the co-oximetry impossible. When the directly measured pO_2 was low there was a small decrease in pO_2 during spinning while pO_2 increased when the pre-spin pO_2 was higher. Simple diffusion of oxygen through the plastic tube would result in the opposite effect. Therefore it must be due to a left shift of the dissociation curve during centrifugation, but neither systematic changes in pH nor pCO_2 were evident. That spinning in itself changes the dissociation curve is unlikely. As intracellular pH are well buffered [35] and changes in erythrocyte volume and/or shape are immediately reversed post-spinning [36] we are left with no evident explanation of our findings. Myers et al. by-passed these problems by creating a dual-layer phantom separating scattering and absorption into two layers [37]. This approach has not been validated. It violates the assumption of tissue homogeneity and possible inter-layer light piping could be an issue. In a similar blood-lipid phantom study validating the NIRO 300 (Hamamatsu Photonics, Hamamatsu City, Japan) the co-oximeter values seem less noisy than in present study, unfortunately the blood sampling procedures are not described in detail [12]. The difficulties with the reference blood co-oximetry prevent final conclusions on the NIRS device – co-oximetry validation.

The present study is to our knowledge the first to compare commercial NIRS devices in a phantom. Interestingly NIRO 300 and INVOS 5100 adult sensor showed linearly correlated values with a large offset of 30.45% and a slope of 0.53, only. This means that the point of equality is 65%, i.e. approximately the normal cerebral oxygenation in adults. Many of the previous clinical studies comparing devices have the drawback of rather narrow oxygenation range. For instance the NIRO 300 and INVOS 4100/5100 adult sensor have been compared several times showing comparable mean values during steady state, but all studies had very few if any $rStO_2$ values below 50% [38–41]. Regarding the difference between the INVOS adult and pediatric sensors, Dullenkopf et al. found a similar mean difference of 11.3 ± 5.37% (SD) between the two sensors, while Pocivalnik found a mean difference of 10% between the NIRO 300 and the INVOS neonatal sensor [42], that has been shown to give similar values to the paediatric sensor [43]. It is thus certain that despite same sensor geometry and LED wavelengths, the INVOS adult sensor gives systematically lower values than the comparable neonatal and paediatric sensors. The neonatal head has a higher water content than the adult head [31] and lower scattering due to less advanced myelination.

It is interesting that all the pair-wise comparisons showed simple linear relations, while the algorithms behind OxyPrem, NIRO and INVOS are different [12,28,44,45]. The OxyPrem and NIRO calculate the difference in attenuation per distance between the two detectors. INVOS subtracts the attenuation at the near detector scaled by a factor that is proportional to the assumed superficial layer thickness from the attenuation at the far detector in order to archieve a signal only from deeper tissue. OxyPrem and NIRO assume wavelength dependent scattering, while this is probably not the case for INVOS. Apparently none of the algorithms account for the tissue water content. Lastly there is the possibility that it simply is a matter of different calibrations. Changing the assumption of superficial layer thickness will change the

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INVOS $rStO_2$ values by an offset and a scaling factor, it is therefore not unlikely that the difference between the INVOS sensors is a matter of different calibrations: " … appropriate scale factors may be determined … for any desired specific application of the methodology disclosed herein, and used to calibrate or correlate the actual output of the implemented apparatus, for example by conventional computer data-processing techniques such as embodying the scale factors in appropriate look-up tables, for example" [45].

A limitation, when comparing or calibrating NIRS devices in a simple phantom, is that the sensor geometry in relation to the multi-layered structure of the human tissue - on the head: skin, scalp, and skull - are not emulated. In that respect it is important to emphasise that the shorter light source-detector distance of the OxyPrem compared to the INVOS could induce differences depending on the tissue interrogated. Future validation of the calibration should include measurements on neonates of different sizes and perhaps also adult heads to examine the generalizability of the calibration. How the differences between the commercial devices identified here will compare to in-vivo use remains to be tested, but it seems unlikely that NIRO 300 and INVOS adult sensor with similar geometry will be in good agreement when the cerebral oxygenation is either very low or very high despite the differences in algorithms Gagnon et al. did find a oxygenation dependent difference between INVOS and NIRO 300 in pigs on cardiopulmonary bypass and induced circulatory arrest [46]. Interestingly we previously found no difference in 'dynamic range' between the same two devices in the adult human forearm using arterial occlusion to achieve a wide range of StO2 values [47].

Clinical use in adults during surgery has removed the issue of poor reproducibility by using pre-surgery SO_2 values as baseline. Our results suggest that treatment guideline stating that interventions should be initiated at a 20 percentage points drop in saturation [48] it should also state on what NIRS device. The trial by Murkin et al. on coronary bypass surgery showed reduced perioperative major organ morbidity and mortality and shorter postoperative hospital stay with INVOS monitoring. If conducted with the NIRO, it is likely to have resulted in fewer interventions, but at more severe desaturations [49].

In conclusion, it was possible to achieve good agreement between a prototype oximeter and a commercial oximeter by simple linear regression over a wide haemoglobin-oxygen saturation range. This is remarkable since the prototype oximeter uses a theory-based algorithm and the commercial instrument uses a proprietary algorithm or look-up table. Two other commercial systems also differed both in the similar simple way.

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